

Leadership in Vaccine Science

Immunization research conducted or sponsored by the National Immunization Program (NIP) includes tracking and monitoring disease, investigating disease outbreaks, evaluating practices for delivering immunization, investigating improved technologies for immunization, and conducting social and behavioral research related to immunization. NIP also prepares immunization recommendations and communicates findings and recommendations to the right audiences. Immunization science addresses this essential question: What can we learn about immunization that helps us protect everyone from vaccine-preventable diseases?

Continuing the Commitment to Immunization Science

Throughout NIP's history, practical, solution-oriented research has been on the rise. Today, more than 200 research projects are underway; of these, almost 80% involve external partners. Even a short list of projects illustrates the breadth of science at NIP. In collaboration with our partners, NIP is investigating

- Impacts of the newer vaccines, such as varicella and pneumococcal, in reducing and eliminating disease as coverage increases
- How well new vaccines work among special populations, such as children with asthma or sickle cell disease
- Better ways to protect infants and adults against diseases such as whooping cough
- The best way to design and conduct studies to uncover any rare adverse events that may follow immunization
- Using computer models to predict the impact of vaccination in the event of a biological attack
- How vaccine shortages affect doctors' practices

- The reasons for racial or ethnic disparities in adult immunization coverage
- Improving the business processes for using computers to track children's vaccinations
- Finding the best ways to translate the success of vaccination to developing countries
- Promoting development of safer, needle-free disposable-cartridge jet injectors (DCJIs) for mass vaccination campaigns and routine immunization
- Conducting clinical vaccine trials of needle-free jet injection to assess the safety, immunogenicity, user preferences, and feasibility of this method

Research for Vaccine Coverage and Effectiveness

NIP staff regularly engage in and publish results of research into vaccine coverage and effectiveness, investigating such areas as the public health and economic impact of vaccines, possible causes and results of under-immunization, and the relation between disease prevention and other important public health issues. In 2004, NIP personnel were

co-authors for over 120 publications about immunization research, included the following significant studies:

- *Low Risk of Measles Transmission after Exposure on an International Airline Flight.* The Journal of Infectious Disease 2004;189(S1):81-5. Following exposure to an infectious patient with measles during a 7-hour flight from Japan to Hawaii, 276 passengers were surveyed. None developed measles. The study suggests that an aggressive response by health departments may not be warranted after airborne exposure to measles.
- *Factors Associated with Under-immunization at 3 Months of Age in 4 Medically Underserved Areas.* Public Health Reports 2004;119(5):479–85. Hepatitis B vaccination rates for high-risk adults are low (30%), and missed opportunities are frequent. Additional strategies are needed to increase immunization rates of adults at high risk for hepatitis B.

- *Racial And Ethnic Disparities in Preschool Immunizations, United States, 1996–2001.* American Journal of Public Health 2004;94(6):973–77. Relatively small but increasing racial and ethnic disparities occur in preschool immunization coverage. The lack of such disparities has been a successful outcome of the Childhood Immunization Initiative; if these disparities continue, they will need to be more actively addressed.
 - *Impact of Thimerosal-Related Changes in Hepatitis B Vaccine Birth-Dose Recommendations on Childhood Vaccination Coverage.* Journal of the American Medical Association 2004;291(19):2351–8. Hepatitis B vaccine coverage dropped when the recommendation to withhold the birth dose was made. After the recommendation was reinstated, coverage rose but did not recover its former level.
 - *Influenza Vaccination of Persons with Cardiovascular Disease in the United States.* Influenza Vaccination and Cardiovascular Disease 2004;31(1):1–6. An analysis of the 1997–2001 National Health Interview Survey data found influenza vaccine coverage among adults aged 18–64 years with cardiovascular disease to be substantially below the national objective of 60%. To improve this coverage, multiple strategies are needed, such as increasing awareness of vaccination by persons with heart disease and the adoption of influenza vaccination by primary care providers and specialists as a standard of care for persons diagnosed with cardiovascular disease.
 - *Impact of Vaccine Shortages on Immunization Programs and Providers.* American Journal of Preventive Medicine 2004;26(1):15–21. As a result of the shortages, more than 85% of immunization programs changed the way they distributed PCV7, DTaP, and Td vaccines to providers, including limiting the amount of vaccine ordered or distributing partial orders. Additionally, 76% of programs reported problems purchasing or receiving varicella vaccine at the time the survey was conducted, and 21% of providers had suspended administration of all doses of PCV7 because they ran out of vaccine before learning of the shortage.
 - *Impact of Health Insurance Status on Vaccination Coverage in Children 19–35 Months Old, United States, 1993–1996.* Public Health Reports 2004; 119(2):156–62. Insurance status was a critical predictor of vaccination coverage for children aged 19–35 months. After controlling for confounding factors, the uninsured were about 24% less likely to receive all recommended vaccines than the insured and, among the insured, those with public insurance are about 24% less likely to receive all recommended vaccines than those with private insurance.
 - *An Economic Analysis of the Current Universal 2-Dose Measles-Mumps-Rubella Vaccination Program in the United States.* The Journal of Infectious Diseases 2004;189(S1):131–45. The current 2-dose MMR vaccination program is cost-saving from both the payers' and societal perspectives compared with the absence of MMR vaccination, with net savings of \$3.5 billion and \$7.6 billion (year 2001 dollars) for one birth cohort, respectively.
 - *Insurance Status and Vaccination Coverage among U.S. Preschool Children.* Pediatrics 2004;113(6):1959–64. This study examined the relationship between immunization coverage levels and insurance status in a national sample of preschool children in the U.S. Insurance status does not appear to be a factor in coverage levels but remains a simple way to identify children at increased risk for under-immunization.
 - *Disruptions in the Supply of Routinely Recommended Childhood Vaccines in the United States.* Pediatrics Infectious Disease Journal 2004;23(6):553–4. This paper examines issues relevant to vaccine shortages that occurred in 2000–2003. The paper summarizes steps taken to manage shortages and recommendations for preventing shortages.
- Other studies investigated the cost-effectiveness of different measles vaccination strategies, measles surveillance in the U.S., factors associated with receiving hepatitis B vaccination, development and use of an algorithm to evaluate suspected smallpox cases, study of household contacts of varicella cases, and the relation between immunization status and the WIC program.

Vaccine Research—Studies in Individual Patients

NIP constantly builds the capacity to research new areas. Initially launched in 2001, the Clinical Immunization Safety Assessment Network, or CISA, takes a new approach to the study of vaccine safety: evaluating individual patients to look for any connections between health concerns and receipt of a vaccine. Because serious side effects of vaccines are so rare, they are difficult to study. Most physicians never see a case; studies of new vaccines cannot enroll enough participants to uncover the rarest side effects. Through CISA, experts at seven large medical centers across the country work to overcome the difficulties of studying rare conditions. For example, researchers at all seven CISA sites monitor cases of certain nervous system conditions to investigate any possible relationship to the use of live-virus vaccines. By pooling resources, researchers may be better able to understand even a one-in-a-million link between a vaccine and a rare reaction.

The centers also provide extensive clinical expertise in evaluating, treating, and managing adverse events following immunization. In the future, primary care providers and subspecialists will be able to refer patients with suspected severe adverse reactions following vaccination to CISA's Clinical Consult Registry and Specimen Repository (CRSR) for standardized patient evaluations and individual recommendations for vaccination care plans. The information from these assessments will supplement knowledge about adverse events following vaccination and help prevent or reduce vaccine-related adverse events.

CISA centers include Johns Hopkins University and the University of Maryland in Baltimore, Maryland; Northern

California Kaiser in San Francisco, California; Stanford University in Stanford, California; Vanderbilt University in Nashville, Tennessee; Boston University Medical Center in Boston, Massachusetts; and Columbia Presbyterian Hospital in New York City, New York.

Vaccine Research—Nationwide Studies

Vaccines must meet the highest accountability standards for safety. CDC researchers, in collaboration with researchers at 8 large managed care organizations, maintain a database of the medical and immunization histories of more than 5.5 million children, adolescents, and adults. This database, called the Vaccine Safety Datalink (VSD), includes more than 1.9% of the U.S. population. Using VSD, researchers can compare health problems between vaccinated and unvaccinated people to help determine whether adverse events following vaccination are causal or coincidental. VSD also permits robust studies of related questions, such as vaccine effectiveness.

In 2004, VSD also completed development of a data-sharing program that allows external researchers to access and analyze data from completed studies in a secure research data center at the National Center for Health Statistics (NCHS).

For detailed information about VSD-based vaccine safety studies, see the *Leadership in Vaccine Safety* section of this report.

New Vaccine Surveillance Network

NIP's success in conducting practical, results-oriented research stems in part from continuing efforts to establish research partnerships and funding opportunities. With the right details in place—the personnel, facilities, and funding—research can be more timely, quickly answering pertinent questions for medical care providers and immunization policy makers.

The New Vaccine Surveillance Network (NVSN), established in 1999, is a recent addition to the many research efforts NIP sponsors. This network of sites investigates the impact of new vaccines and new vaccine policies on children who are hospitalized or are seen in emergency departments or outpatient settings. Along with other studies, NVSN is currently analyzing the burden of respiratory disease among young children. Researchers working in 9 counties in 3 areas (Rochester, New York; Cincinnati, Ohio; and Nashville, Tennessee) discovered that children under age 5 are hospitalized for acute respiratory illness at the rate of 18 out of every 1,000 children, with respiratory syncytial virus (RSV) infections, parainfluenza, and influenza causing most of the disease. These data, supporting a high rate of hospitalization associated with influenza, were instrumental in a 2003 policy change to recommend flu vaccination routinely for all children age 6–23 months. This recommendation took effect in the fall of 2004. Vaccines for RSV and parainfluenza are both in clinical trials. In the future, the NVSN should note a marked reduction in the number and severity of acute respiratory illnesses thanks to recommended vaccinations.

Applied Research and Development

Vaccine Research Conference

CDC is a co-sponsor of this annual conference, which has become the largest scientific meeting devoted exclusively to the research and development of vaccines and associated technologies for disease control through immunization. Since its inception in 1998, the conference has attracted an average of more than 400 participants from 48 countries each year. The conference covers basic vaccine science, product development, and clinical and field studies. Those who attend the conference have an opportunity to share scientific advances that contribute to the development of vaccines and to identify research opportunities associated with vaccine development, production, and distribution.

Topics at the seventh conference, held in Arlington, Va., May 24–26, 2004, included SARS, vaccine technologies for developing nations, vaccine safety, immunomodulators and immune response assessment, needle-free vaccination, genomics for vaccine research and development, and vaccines for new and emerging pathogens. The next Vaccine Research Conference is scheduled for May 9–11, 2005, in Baltimore, MD. Visit www.nfid.org/conferences/vaccine05/ for more information.

Success Stories in Applied Research

Safer Injection Technology

Researchers are working to reduce the drawbacks and limitations of vaccination with conventional needle and syringe. Through Small Business Innovation Research (SBIR) contracts, a new generation of safe, needle-free, high-speed jet injector immunization devices is being developed. These devices could be used for rapid protection of a population against vaccine-preventable diseases (such as mass campaigns to eradicate measles), for control of epidemics of meningococcal disease and pandemics of high-mortality influenza, and to help respond to some forms of bioterrorism. In 2004, working prototypes were demonstrated at the World Health Organization in Geneva and at other meetings. In November, they were taken to Tanzania and South Africa by the Program for Appropriate Technology in Health to conduct user ergonomics trials among health workers and to gather feedback from typical users to guide further design refinements.

Safer Disposal of Vaccination Waste

SBIR contracts are also funding three companies to design simpler, more affordable melter ovens for developing countries to reduce needle-syringe waste to plastic bricks that safely embed the needles and can be recycled for building material or other uses.

Other Safe Technology Activities

Additional activities include participation in conferences and international standards development for jet injection, setting priorities for research and development for new vaccine administration technologies on behalf of the World Health Organization, and maintaining a comprehensive website (www.cdc.gov/nip/dev) and news service (<http://vaxdex.forum.cdc.gov>) on needle-free administration of drugs.

Aerosol Vaccination Device

Aerosol vaccination has been shown to be an effective way to deliver measles vaccine; however, the equipment for aerosol vaccination is cumbersome and has many technical limitations. NIP has developed VaccinAire™, an aerosol vaccination device that overcomes previous limitations and is designed for mass measles vaccination. Through a Small Business Innovation Research contract, the device is being refined, and manufacture of clinical trial prototypes and testing are in progress. CDC has applied for a patent and is negotiating with a private company to license, manufacture, and distribute the VaccinAire™ device.

Laboratory tests show the handheld battery-powered prototypes deliver live measles vaccine aerosols without loss of potency. Several animal studies have confirmed the safety and immunogenicity of measles vaccine delivered by the device, including a full toxicology study which demonstrates immunogenicity with no adverse events and no tissue pathology. Clinical trials are expected to begin in 2005.



A young girl is vaccinated with a jet-injector gun in 1971.

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The new generation jet-injector (2004).